REMARKS

Claims 15, 16, 20, 21, 29, 30, 42, 45-49, 51, 54, and 55 are pending. Due to a Restriction Requirement, all pending claims except claim 29 have been withdrawn from consideration. In the final Office action mailed April 19, 2007, claim 29 was examined. Claim 29 stands rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter. Claim 29 is also rejected under 35 U.S.C. § 103 as unpatentable over Seino et al., *Ann. Surg.* 234:681-688, 2001 (hereafter "Seino") in view of Heinke et al., *Cardiovasc. Res.* 49:127-134, 2001 (hereafter "Heinke") and, further, as unpatentable over Chao et al., *J. Biol. Chem.* 277:31639-31645, 2002 (hereafter "Chao"). The specification is objected to for reciting an incorrect claim status indicator. The objection and each rejection are addressed below.

Objection to the specification

The claim listing filed with reply mailed January 29, 2007 is objected for indicating that claims 49 and 51 are "original" rather than "withdrawn." This has been corrected in the claim listing filed herewith. Accordingly, Applicants request that this objection be withdrawn.

Rejection under 35 U.S.C. § 101

The Office asserts that claim 29 is directed to non-statutory subject matter. Despite Applicants' prior amendment to the claim to recite a recombinant dominant negative FADD (dn-FADD), the Office asserts that a cardiomyocyte expressing recombinant dominant negative FADD is a product of nature, because recombination can naturally occur. The bar to patentability under 35 U.S.C. § 101 excludes that which is not made by man. As the cardiomyocytes of the present invention were made by man, these cells constitute patentable subject matter under the statute. Applicants respectfully request this rejection be withdrawn.

Rejection under 35 U.S.C. § 103 - Seino in view of Heinke

A conclusion of nonobviousness must be reached if the claimed invention provides an unexpected advantage or advantages and the prior art teaches away from the combination which is now claimed. Indeed, the M.P.E.P. (§ 2145, eighth edition, revision 6) indicates that a showing of unexpected results is usually sufficient to overcome a *prima facie* case of obviousness. In view of the results shown in the present specification and the teachings of the prior art, Applicants submit that the cardiomyocytes expressing dn-FADD of claim 29 are patentable.

The cited art does not teach that FADD or dn-FADD can reduce inflammation

The art cited by the Office fails to teach or suggest an important feature of the present invention, namely that expression of dn-FADD in cardiomyocytes decreases both apoptosis and inflammation through inhibition of NF-κB activation. To highlight the importance of this feature, Applicants have amended claim 29 to recite that the expression of dn-FADD is capable of preventing or reducing inflammation. Support for this change is found throughout the specification, for example, at page 6, line 11. This amendment adds no new matter.

The art does not teach or suggest the possibility of dn-FADD reducing inflammation. Indeed, the references cited by the Office in its § 103 rejection, Seino and Heinke, not only fail to teach this feature of the present invention, but instead suggest the opposite to be true. In particular, the liver cells of Seino show that dn-FADD expression results in no loss of NF-κB activation, in sharp contrast to the inhibition of NF-κB activation observed in cardiomyocytes expressing dn-FADD. The teaching of Seino would therefore suggest that dn-FADD has little, if any, effect on the inflammatory response. This deficiency cannot be, and is not, remedied by Heinke, which is unconcerned with inflammation. Heinke only notes that the pacing model of heart failure in dogs results in apoptotic cell death. Thus, one of skill in the art simply could not conclude from either of these references that dn-FADD expression would reduce inflammation in cardiomyocytes.

Further, the prior art indicates that the effect of FADD or dn-FADD expression is highly cell-type specific. The present application shows that FADD and dn-FADD can reduce NF-κB activity (see, e.g., page 32, line 24 through page 33 line 14 of the specification) in cardiomyocytes. Seino, as noted above, teaches no effect of dn-FADD on NF-κB activation. By contrast, expression of FADD in HeLa cells activates NF-κB (see page 15, lines 6-15 of the specification, citing Wajant et al., *J. Biol. Chem.* 275:24357-24366, 2000). These results would suggest that expression of FADD or dn-FADD may either have no effect or may increase an inflammatory response, and would thus be unsuitable for use in the present invention. In view of the art, the reduction of inflammation in cardiomyocytes is indeed surprising.

The data presented in the specification confirms the cell-type specific effects of FADD and dn-FADD expression. Experiments in human umbilical cord vein endothelial cells and rat pulmonary artery cells expressing dn-FADD did not result in inhibition of NF-κB activation (see, e.g., page 33, lines 16-28 of the specification and Figures 9A and 9B). These results likewise suggest that one could not have predicted *a priori* that expression of dn-FADD in a cardiomyocyte would reduce inflammatory response.

dn-FADD suppression of <u>both</u> apoptosis and inflammation is completely unexpected

Even if one of skill in the art thought that dn-FADD would suppress NF-κB activation in cardiac cells, the art would still teach away the claimed invention. Mustapha

et al. (*Am. J. Physiol. Heart Circ. Physiol.* 279:H939-H945, 2000 as cited on page 16, lines 18-19 of the specification) indicates that inhibiting NF-κB activity can potentiate, rather than reduce, apoptosis in cardiac cells. This reference therefore suggests that minimizing cardiac inflammation through the NF-κB pathway may undesirably exacerbate apoptosis. The present result, i.e., that dn-FADD expression caused a reduction in both inflammation and apoptosis, is therefore completely unexpected.

For the reasons described above, it would not have been obvious to combine the teachings of Seino and Heinke as proposed by the Office. The results of dn-FADD expression in cardiomyocytes are completely surprising in view of the Seino, Heinke, and the art described herein, and the results of dn-FADD and FADD expression in other cell types. Applicants therefore request that the § 103 rejection in view of Seino and Heinke be withdrawn.

Rejection under 35 U.S.C. § 103 - Chao

The Office maintains the rejection of claim 29 as obvious in view of Chao. Applicants again provide an unsigned Declaration under 37 C.F.R. § 1.131 of Dr. Anthony Rosenzweig in support of this traverse. Upon receipt of the signed Declaration, Applicants respectfully submit that this rejection may be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the final Office action for three (3) months, to and including October 19, 2007, and a check in payment of the required extension fee. Also enclosed is a Notice of Appeal.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045